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10/758,554	01/14/2004	Christine Lindsay Mummery	17360	5975

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SCULLY SCOTT MURPHY & PRESSER, PC
400 GARDEN CITY PLAZA
SUITE 300
GARDEN CITY, NY 11530

EXAMINER	
SGAGIAS, MAGDALENE K	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,554	MUMMERY, CHRISTINE LINDSAY	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45,46,49-55,60-65,68-71 and 87-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-46, 49-55, 60-65, 68-71, 87-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 10/29/07 have been fully considered. The amendment has been entered. Claims 45-46, 49-55, 60-65, 68-71, 87-91 are pending and under consideration. Claims 1-44, 47-48, 56-59, 66-67, 72-86, 92-132 are canceled.

Claim Objections

Claims 68, 69, 90, 91 objection under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim is depended on non-elected claim is withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 45-46, 62-64, 71, 87-88 rejection under 35 U.S.C. 102(b) as being anticipated by Wobus et al, (Roux's Arch Dev Biol, 204: 36-45, 1994) is withdrawn.

Claims 45-46, 70, 87 rejection under 35 U.S.C. 102(b) as being anticipated by Wobus et al, (J Mol Cell Cardiol, 29: 1525-1539, 1997) is withdrawn.

Claims 45-46, 49-51, 53-54, 60-63 rejection under 35 U.S.C. 102(b) as being anticipated by Mummery et al, (Differentiation, 46: 51-60, 1991) is withdrawn.

Claim 90 rejection under 35 U.S.C. 102(b) as being anticipated by Rohwedel et al, (Dev Biol, 29: 164(1): 87-101, 1994) is withdrawn.

Claim 91 rejection under 35 U.S.C. 102(b) as being anticipated by Mummery et al, (Differentiation, 46: 51-60, 1991) is withdrawn.

Claims **45-46,, 62, 63, 64, 71, 87, 88, 89** are rejected under 35 U.S.C. 102(b) as being anticipated by **Itskovitz-Eldor et al,** (Molecular Medicine, 6(2): 88-95, 2000).

Itskovitz-Eldor et al teach a method for inducing differentiation of a undiffentiated human embryonic stem (hES) cell into a mesodermal cell comprising culturing the hES cell in the presence of a mouse embryonic stem cell under conditions that induce differentiation of the undifferentiated human stem cell into the mesoderm cell, wherein the human embryoid bodies (EBs) show characteristic regional expression of embryonic markers specific for to different lineages, namely, ζ-globin (mesoderm) (p 88, 2nd column, 1st paragraph, and p 89, under materials and methods) **(claims 45, 88).**

Itskovitz-Eldor et al teach a method for obtaining a cell population comprising a sub-population of differentiated cells of a mesodermal lineage wherein the differentiated cells are derived from undifferentiated hES cells in the cell population by culturing the hES cell in the presence of a mouse embryonic stem cell under conditions that induce differentiation of the undifferentiated human stem cell into the mesoderm cell, wherein the human embryoid bodies (EBs) show characteristic regional expression of embryonic markers specific for to different lineages, namely, ζ-globin (mesoderm), neurofilament (ectoderm), and α-fetoprotein (endoderm) (p 88, 2nd column, 1st paragraph) (**claims 46, 88**).

Itskovitz-Eldor et al teach said method, wherein the subpopulation consists of cardiomyocytes, where in Fig. 4, demonstrate a large vacuolated embryoid body, including cardiac muscle cell layers, and in situ hybridization of sections from this EB with a probe for α-cardiac actin, a marker of embryonic myocardial cells, revealed that the central cavity was surrounded by cardiac muscle cells (Fig. 4C) (**claims 46, 62, 63, 64, 71, 87, 89**).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 55, 65, 89 rejection under 35 U.S.C. 103(a) as being unpatentable over Mummery et al, (Differentiation, 46: 51-60, 1991) in view of Mummery et al, (Biochem Biophys Res Commun, 191(1): 188-195, 1993) is withdrawn.

Claims **45-46, 49-55, 60-65, 68-71, 87-91** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Itskovitz-Eldor et al,** (Molecular Medicine, 6(2): 88-95, 2000) in view of **Sugi et al,** (Developmental Dynamics, 200: 155-162, 1994); **Zhu et al,** (Developmental Dynamics, 207: 429-438, 1996); **Lough et al,** (Developmental Dynamics, 217: 327-342, 2000); **Klug et al,** (J Clin Invest, 98: 216-224, 1996).

Itskovitz-Eldor et al teach a method for inducing differentiation of a undiffentiated human embryonic stem (hES) cell into a mesodermal cell comprising culturing the hES cell in the presence of a mouse embryonic stem cell under conditions that induce differentiation of the undifferentiated human stem cell into the mesoderm cell, wherein the human embryoid bodies (EBs) show characteristic regional expression of embryonic markers specific for to different lineages, namely, ζ-globin (mesoderm) (p 88, 2nd column, 1st paragraph, and p 89, under materials and methods) **(claims 45, 88).**

Itskovitz-Eldor et al teach a method for obtaining a cell population comprising a sub-population of differentiated cells of a mesodermal lineage wherein the differentiated cells are derived from undifferentiated hES cells in the cell population by culturing the hES cell in the presence of a mouse embryonic stem cell under conditions that induce differentiation of the

undifferentiated human stem cell into the mesoderm cell, wherein the human embryoid bodies (EBs) show characteristic regional expression of embryonic markers specific for to different lineages, namely, ζ-globin (mesoderm), neurofilament (ectoderm), and α-fetoprotein (endoderm) (p 88, 2nd column, 1st paragraph) (**claims 46, 88**).

Itskovitz-Eldor et al teach said method, wherein the subpopulation consists of cardiomyocytes, where in Fig. 4, demonstrate a large vacuolated embryoid body, including cardiac muscle cell layers, and in situ hybridization of sections from this EB with a probe for α-cardiac actin, a marker of embryonic myocardial cells, revealed that the central cavity was surrounded by cardiac muscle cells (Fig. 4C) (**claims 46, 62, 63, 64, 71, 87, 89**). **Itskovitz-Eldor et al** suggest that the in vitro differentiation of human ES cells into specific lineages can serve as a source of mature cells, which may be used in cell transplantation and offer an opportunity to study in vitro processes involved in early human embryogenesis. **Itskovitz-Eldor et al** differ from the present invention for not teaching the embryonic stem cell is an endodermal or ectodermal cell or tissue.

However, at the time the claimed invention was made, **Sugi et al,** teach the effect of anterior endoderm/mesoderm precardiac co-culture on terminal differentiation of cardiomyocytes in vitro (p 158, Table 1). Sugi teaches the co-explanted, germ layers of anterior endoderm/mesoderm resulted in 12/12 number of contractile explants/number of total explants versus co-cultured germ layers of individually explanted, resulted in equivocal 12/13 number of contractile explants/number of total explants (p 158, Table 1). Sugi suggests that cells of the anterior endoderm/mesoderm specifically regulate the terminal differentiation of cardiomyocytes (p 159, 2nd column, last paragraph bridge p 160, 1st column, 1st paragraph). Sugi shows that only anterior endoderm cells were able to cause terminal differentiation in stage 6 mesoderm (p 156, 1st column, 3rd paragraph). Sugi demonstrates that stimulation of cardiogenesis by anterior

endoderm was observed when the germ layers were co-cultured as a contiguous co-explant and when the germ layers were separated and co-cultured at opposite sides of the culture dish (figures 1 and 2). Sugi also describes a distance as long as 2 mm separated the germ layers at the commencement of the culture period. Sugi suggests the need to co-culture said explants separated by semi-permeable membrane (p 158, bridge 1st and 2nd column). Sugi teaches that the anterior endoderm cells regulate the terminal differentiation as opposed to the growth of presumptive cardiac myocytes in mesoderm from the anterior lateral plate (abstract). As such, Sugi et al provide sufficient motivation for one of ordinary skill in the art to apply the endodermal embryonic cells of the Sugi into the hES cells culture system of **Itskovitz-Eldor et al** for inducing differentiation of a undiffentiated hES cells by culturing the hES cell in the presence of endodermal culture conditions for the induction of differentiation of undifferentiated hES cells.

It would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the culture conditions of **Itskovitz-Eldor et al**, by co-culturing hES cells with mesodermal, endodermal cells or both to induce terminal differentiation of the undifferentiated hES cells as taught by Sugi. One of ordinary skill in the art would have been sufficiently motivated to make such a modification **Itskovitz-Eldor et al** suggest that the in vitro differentiation of human ES cells into specific lineages can serve as a source of mature cells, which may be used in cell transplantation and offer an opportunity to study in vitro processes involved in early human embryogenesis and in view of Sugi showing anterior endoderm effects terminal differentiation of cardiac myocytes in vitro under co-culture conditions of endoderm/mesoderm explants.

Itskovitz-Eldor et al taken with Sugi et al do not teach the embryonic cell is derived from visceral endoderm tissue or derived from visceral endoderm-like tissue, or derived from an early post-gastrulation embryo or wherein the visceral endoderm-like tissue is an embryonic cell

line or wherein the embryonic cell line is an END-2 cell line or wherein the embryonic cell line is derive from mouse embryo E7.5.

However, at the time of the instant invention **Zhu et al,** teach the expanding list of endoderm-derived growth factors that enable precardiac mesoderm to complete terminal differentiation include FGF-1 and FGF-4 and it is not surprising considering the effects of heart forming region endoderm on heart development are complex involving the concerted action of multiple agents (p 434, 1st column, last paragraph). Lough et al supplements the findings of Zhu et al by teaching there is a relationship between endoderm cells and the development of cardiac tissue from mesoderm and an interaction between the endoderm and mesoderm during the specification (a state of cellular differentiation in which the differentiative outcome cannot be altered) and terminal differentiation of myocardial cells and endoderm-derived molecules regulate the formation of both myocardial and endocardial cells during terminal differentiation of cells in developing embryonic heart (abstract). **Lough et al,** while reviewing the role of endoderm in the heart development and the role of endoderm in cardiomyocyte differentiation noted an inductive role for definitive endoderm is in accord with experiments demonstrating that co-explanted *Xenopus* endoderm and Spemann organizer can synergistically induce cardiogenesis in embryonic mesoderm that is undergoing erythropoiesis and that late gastrulation stage avian anterolateral (AL) definitive endoderm, but not posterior mesendoderm, induces cells in stage 4 posterior primitive streak (PPS) (p 329, 2nd column). **Lough et al,** teach that anterolateral endoderm can also induce cardiogenesis in stage 6 posterolateral mesoderm similar to its ability to induce cardiogenesis in these cells' PPS progenitors (p 329, 2nd column). Lough et al teach in mammals, formation of the definitive endoderm is similar, with the primitive visceral endoderm serving as the homologue of the avian hypoblast and although most experiments performed using the avian model attribute cardiogenic activity to the definitive

anterolateral endoderm, recent findings using the mouse embryo indicate that cardiac inductive activity resides in the anterior visceral endoderm (AVE) (p 217, 2nd column, 1st paragraph). Lough et al teach because the avian definitive endoderm and the extraembryonic (hypoblast) endoderm layers are contiguous, the possibility should be considered that the extraembryonic endoderm, in areas adjacent to the definitive embryo, participates in the cardiogenic process (p 217, 2nd column, 1st paragraph). Lough also teaches that VEGF has a prominent role in the assembly of endocardial precursor cells (p 337, columns 1-2, p 338, Table 1). Lough also teaches that among anterolateral endoderm-derived growth factors that may regulate the formation of endocardium from precardiac mesoderm, TGFbs induce endocardial precursor cells as assessed by the formation of invasive mesenchymal cells that express QH-1; by contrast, VEGF functions to assemble these cells into a vascular-like epithelial structure (p 338, 1st column under summary). Lough et al conclude that these endoderm-derived growth factors differentially affect processes of endocardiogenesis and cardiac myogenesis in specified precursor cells that reside in precardiac mesoderm.

Thus, it would also have been obvious for one of ordinary skill in the art of inducing differentiation of hES cells into cardiomyocytes to further employ visceral endoderm tissue or post-gastrulation embryo derived tissue or cells derived from mouse embryo and further include culturing the mouse endoderm cells in the presence of VEGF of the combined cited reference. One of ordinary skill in the art would have been motivated to employ the visceral endoderm tissue or cells from visceral endoderm derived from a mouse embryo and in the presence of VEGF in order to enable precardiac mesoderm cells to complete terminal differentiation in the presence of VEGF considering the effects of endoderm on heart development and cardiomyocyte differentiation in view of the totality of the prior art at the time the invention was made.

Itskovitz-Eldor et al taken with Sugi et al, taken with **Zhu et al taken with Lough et al,** do not teach a hES cell genetically modified.

However, at the time the invention was made, **klug** is an exemplified prior art that teaches that it is routine or well-established in the art to employ genetically selected cardiomyocytes from differentiating embryonic stem cells form stable intracardiac grafts (title). Klug teaches a selection procedure applicable to all ES-derived cell lineages, provided that suitable cell type–specific promoters are available and suggest that given that numerous cell lineages of ecto-, endo-, and mesodermal origin are represented in differentiating ES cultures, it is likely that ES derived cellular transplantation strategies can be extended to other organ systems and ES lines capable of cardiogenic differentiation have been generated in a number of species, including mouse, rat, rabbit, mink, pig, and most recently primates and cardiomyocyte engraftment may proves to be of therapeutic value, the generation of cardiogenic human ES cell lines would preclude the requirement for either human fetal or xenotrophic tissue and the existence of pluripotent human embryonic carcinoma cell lines is encouraging with regards to the prospects of generating cardiogenic human ES cells (p 223, 1st column, last paragraph).

Thus, it would also have been obvious for one of ordinary skill in the art of inducing differentiation of undiffentiated hES into a cardiomyocyte to further employ genetically modified hES cells of the combined cited reference. One of ordinary skill in the art would have been motivated to employ genetically modified hES cells in order to generate cardiogenic human ES cells for grafting as suggested by Klug and in view of the totality of the prior art at the time the invention was made.

Thus, the claimed invention as a whole is clearly prima facie obvious in the absence of evidence to the contrary.

Applicants arguments are moot in view of the new rejections.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The double patenting rejection is maintained for reasons of record in the previous office action page 9 mailed 4/27/07.

Applicants argue that the claims as amended are patentably distinct over claim 1 of "790. These arguments are not persuasive because both sets of claims are embrace induction of differentiation of undifferentiated stem cells.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter

Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Sgagias, Ph.D.
Art Unit 1632

/Anne-Marie Falk/
Anne-Marie Falk, Ph.D.
Primary Examiner, Art Unit 1632